[Chem. Pharm. Bull. 36(9)3348—3353(1988)]

Quinolizidines. XXV.[1] An Extension of the "Lactim Ether Route" to the Racemic Syntheses of Several Indolo[2,3-*a*]quinolizidine Alkaloids

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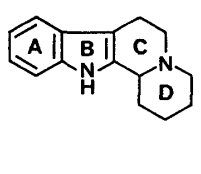
(Received March 9, 1988)

The "lactim ether route," originally designed for unified racemic and chiral syntheses of the benzo[*a*]quinolizidine-type *Alangium* alkaloids, has been extended to cover the racemic syntheses of several indolo[2,3-*a*]quinolizidine alkaloids (**1** and **8c, d**). The synthetic routes started from the lactams **5a, b** and proceeded smoothly through the lactim ethers **6a, b**, lactam ketones **7a, b**, lactam alcohols **10a, b**, and *N*-substituted lactams **9a, b**.

Keywords——indoloquinolizidine alkaloid synthesis; *Corynanthe* alkaloid; *N*-substituted lactam; lactim ether alkylation; sodium borohydride reduction; catalytic hydrogenolysis; Bischler–Napieralski cyclization

The indole alkaloids, a large and complex group of natural products bearing the indole or 2,3-dihydroindole (indoline) ring in their structures, include a number of indolo[2,3-*a*]-quinolizidine alkaloids (*e.g.*, **1**), often referred to as indoloquinolizidine alkaloids.[2] Although the chemical structures of most of the known indoloquinolizidine alkaloids have been unequivocally established, there are some structural problems still remaining even in this new era of highly refined spectroscopic studies.[2c] Solutions to these problems could come with the racemic and/or chiral syntheses of compounds possessing the candidate structures, and the syntheses might be feasible through the "lactim ether route",[3] which has proved



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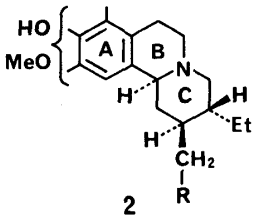

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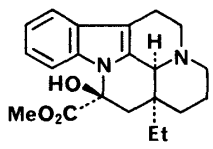

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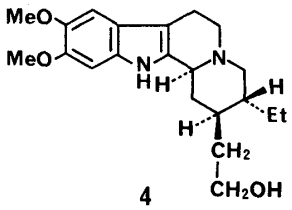

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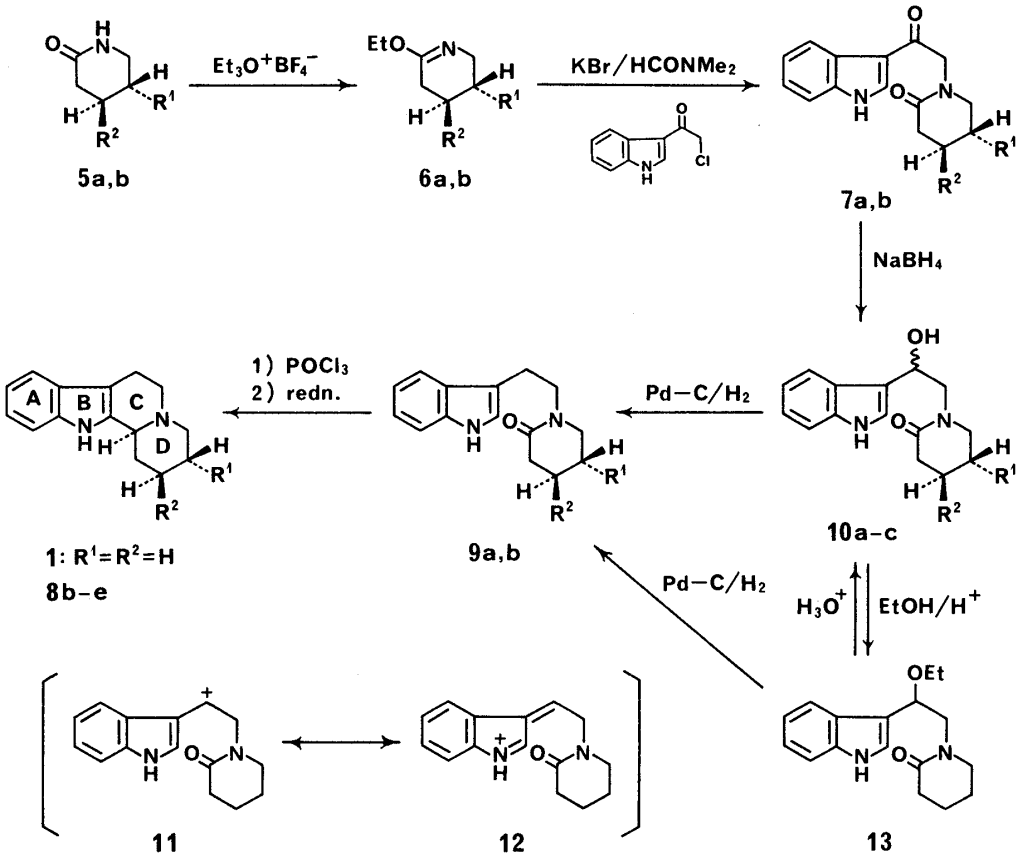
useful and effective for the racemic and chiral syntheses of the structurally analogous benzo[*a*]quinolizidine-type *Alangium* alkaloids (type **2**).[3d,4] In the present work, the feasibility of such a synthetic approach was tested in the racemic syntheses of several of the known indoloquinolizidine alkaloids, such as **1** and **8c, d**.[5]

Alkylation of the lactim ether **6a**, obtained in 84% yield from the unsubstituted lactam **5a** according to the literature procedure,[3a,6] with 3-(chloroacetyl)indole in $HCONMe_2$ at 60 °C in the presence of KBr for 24 h furnished the lactam ketone **7a** in 71% yield. In the absence of KBr, the progress of alkylation was extremely slow, suggesting the intermediary formation of 3-(bromoacetyl)indole in the above alkylation. Reduction of **7a** with $NaBH_4$ in aqueous EtOH at room temperature for 20 h gave the lactam alcohol **10a** (96% yield), which was then hydrogenolyzed (10% Pd–C/H_2, 20 °C, 1 atm, 50 min) in EtOH containing a small amount of



a: $R^1=R^2=H$ b: $R^1=Et$; $R^2=CH_2CO_2Et$ c: $R^1=Et$; $R^2=CH_2CH_2OH$

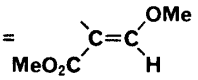
d: $R^1=Et$; $R^2=$  e: $R^1=Et$; $R^2=$ 

Chart 1

70% aqueous $HClO_4$ to afford the known lactam **9a**[7] in 96% yield. The hydroxy group of **10a** at the indolylcarbinyl carbon was found to be considerably reactive. On treatment with EtOH in the presence of a catalytic amount of HCl at 25 °C for 1 h, **10a** produced the ethoxy derivative **13** in 94% yield. Conversely, treatment of **13** with H_2O in MeCN containing a catalytic amount of HCl at 17 °C for 1 h reproduced the lactam alcohol **10a** in 86% yield. These transformations reflect the acid-catalyzed formation of the reactive "3-indolylcarbinyl system"[8] (**11**↔**12**) from **10a** and from **13**. Catalytic hydrogenolysis of **13** to give **9a** was smoothly effected under reaction conditions similar to those employed for the above conversion of **10a** into **9a**, but the result was less satisfactory when the reaction was carried out in the absence of $HClO_4$.

Bischler–Napieralski cyclization of the lactam **9a** ($POCl_3$, boiling benzene, 75 min)[7] and reduction of the resulting quaternary salt ($NaBH_4$, MeOH, 1 h)[7] provided the tetracyclic base **1** (95% overall yield from **9a**), which was identical with an authentic sample.[7] The tetracycle **1** is the simplest member of the indoloquinolizidine alkaloids: Its (−)-isomer, yet unnamed, has been isolated[9] in partially racemized form from the leaves of a New Guinea tree, *Dracontomelum mangiferum* BL., belonging to the family Anacardiaceae. Although more than 30 synthetic routes to this parent framework (**1**) have been reported,[7,10] our "lactim ether route" described above may be of value, not only in preparing the alkaloid material (**1**) in an

acceptable overall yield but also in the design and execution of the total syntheses of analogous alkaloids carrying substituents in ring A and/or ring D.

In order to evaluate the applicability of the "lactim ether route" to synthesis of more complex indoloquinolizidine alkaloids, we next tried to synthesize (±)-dihydrocorynantheine (**8d**) and related alkaloids from the (±)-*trans*-lactam ester **5b**. The starting material **5b**[11] was first converted into the lactim ether **6b** in excellent yield by an ethylation method given in the literature.[12] Treatment of **6b** with 3-(chloroacetyl)indole in $HCONMe_2$ at 60 °C in the presence of KBr for 38 h gave the lactam ketone **7b** in 70% yield. Reduction of **7b** with $NaBH_4$ (EtOH, 22—25 °C, 3 h) furnished a diastereomeric mixture of the lactam alcohol **10b** in 70% yield. Prolonged reduction in this case was found to lower the yield of **10b** owing to the formation of a by-product presumed to be a diastereomeric mixture of the diol **10c**. The diastereomeric mixture **10b** was then submitted to hydrogenolysis (10% Pd–C/H_2, EtOH, 1 atm, 21—22 °C, 1 h) in the presence of a small amount of 70% aqueous $HClO_4$ to afford the (±)-*trans*-lactam ester **9b** (74% yield), which was identical with an authentic sample.[13] The lactam ester **9b** has been converted into (±)-dihydrocorynantheine (**8d**)[13,14] and (±)-dihydrocorynantheol (**8c**)[15] through the (±)-tetracyclic ester **8b**[13] (and (+)-dihydrocorynantheine [(+)-**8d**] has been shown to lead to (−)-dihydrositsirikine [(+)-**8e**][16]). Consequently, the above results (**5b**→**6b**→**7b**→**10b**→**9b**) imply that an alternative synthesis of each of these alkaloids has now been completed in a formal sense.

In summary, the scope of our "lactim ether route",[3] originally designed for unified racemic and chiral syntheses of the benzo[*a*]quinolizidine-type *Alangium* alkaloids,[3d,4] has now been enlarged to include the syntheses of the indoloquinolizidine-type analogues. Interestingly, after the disclosure[5] of a summary of the present work, Govindachari's group has reported that this route was also effective for the synthesis of (±)-vincamine (**3**).[17] Other successful applications in the *Corynanthe*-type indoloquinolizidine series are seen in our recent racemic and chiral syntheses of ochropposinine (**4**),[18] which unequivocally established the structure and absolute stereochemistry of this *Ochrosia* alkaloid.

Experimental

General Notes——All melting points were determined by using a Yamato MP-1 capillary melting point apparatus and are corrected. Unless otherwise noted, the organic solutions obtained after extraction were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. Spectra reported herein were recorded on a Hitachi 323 ultraviolet (UV) spectrophotometer, a JASCO IRA-2 infrared (IR) spectrophotometer, a JEOL JMS-01SG mass spectrometer, or a JEOL JNM-PS-100 nuclear magnetic resonance (NMR) spectrometer at 23 °C with Me_4Si as an internal standard. Elemental analyses were performed by Mr. Y. Itatani and his associates at Kanazawa University. The following abbreviations are used: br = broad, m = multiplet, q = quartet, s = singlet, sh = shoulder, t = triplet.

1-[2-(1*H*-Indol-3-yl)-2-oxoethyl]-2-piperidinone (7a)——A solution of **6a**[3a,6] (12.59 g, 99 mmol) and 3-(chloroacetyl)indole[19] (17.40 g, 90 mmol) in $HCONMe_2$ (20 ml) containing KBr (12.85 g, 108 mmol) was stirred at 60 °C for 24 h. After cooling, the reaction mixture was poured into a mixture of H_2O (400 ml) and AcOEt (100 ml). The precipitate that resulted was filtered off, washed successively with H_2O (100 ml) and AcOEt (80 ml), and dried to give **7a** (13.44 g) as a brown powder, mp 235.5—236.5 °C. The AcOEt layer separated from the filtrate was washed with H_2O (150 ml), dried, and concentrated to leave a brown oil. The oil was triturated with MeCN (80 ml), and the insoluble solid that resulted was collected by filtration and dried to yield a second crop (2.97 g) of **7a**, mp 235—236 °C. The total yield was 16.41 g [71% yield based on the 3-(chloroacetyl)indole used]. Recrystallization of the solid from MeCN gave an analytical sample as colorless pillars, mp 240—241 °C; MS *m/z*: 256 (M^+); UV λ_{max}^{EtOH} 242 nm (ε 13200), 260 (sh) (9000), 299 (12800); IR ν_{max}^{Nujol} cm^{-1}: 3120, 3080 (NH), 1648 (ArCO), 1607 (lactam CO); NMR (Me_2SO-d_6) δ: 1.48—1.88 (4H, m, $H_{(4)}$'s and $H_{(5)}$'s), 2.06—2.40 (2H, m, $H_{(3)}$'s), 3.10—3.40 (2H, m, $H_{(6)}$'s), 4.60 (2H, s, $COCH_2N$), 6.94—8.32 (5H, m, aromatic protons), 11.80 (1H, br s, NH). *Anal.* Calcd for $C_{15}H_{16}N_2O_2$: C, 70.29; H, 6.29; N, 10.93. Found: C, 70.15; H, 6.28; N, 10.83.

1-[2-Hydroxy-2-(1*H*-indol-3-yl)ethyl]-2-piperidinone (10a)——i) By Reduction of **7a**: A solution of **7a** (500 mg, 1.95 mmol) in 80% (v/v) aqueous EtOH (50 ml) was stirred under ice-cooling, and $NaBH_4$ (370 mg, 9.76 mmol) was added portionwise. After the mixture had been stirred at 14—20 °C for 20 h, acetone (3 ml) was added under ice-cooling. The resulting mixture was further stirred for 10 min and then concentrated *in vacuo*. The residue was treated

with H_2O (20 ml), and the aqueous mixture was neutralized with 10% aqueous HCl. The precipitate that resulted was filtered off, washed with H_2O, and dried to give **10a** (490 mg, 96%) as a colorless powder, mp 177—179 °C. Recrystallization from EtOH produced an analytical sample as colorless prisms, mp 178—179 °C; MS *m/z*: 258 (M^+); UV λ_{max}^{EtOH} 274 nm (sh) (ε 5850), 282 (6300), 290 (5500); IR ν_{max}^{Nujol} cm^{-1}: 3200 (NH and OH), 1600 (lactam CO); NMR (Me_2SO-d_6) δ: 1.32—1.84 (4H, m, $H_{(4)}$'s and $H_{(5)}$'s), 2.08—2.40 (2H, $H_{(3)}$'s), 2.84—3.84 [4H, m, $H_{(6)}$'s and $CH(OH)C\underline{H}_2N$], 4.92—5.36 [2H, m, $C\underline{H}(O\underline{H})CH_2N$], 6.80—7.76 (5H, m, aromatic protons), 10.56 (1H, br s, NH). *Anal.* Calcd for $C_{15}H_{18}N_2O_2$: C, 69.75; H, 7.02; N, 10.84. Found: C, 69.48; H, 7.01; N, 10.86.

ii) By Hydrolysis of **13**: A solution of **13** (258 mg, 0.9 mmol) in 50% (v/v) aqueous MeCN (7 ml) containing 0.02 N aqueous HCl (2 ml) was stirred at 17 °C for 1 h. After addition of 10% aqueous Na_2CO_3 (1 ml), the reaction mixture was concentrated *in vacuo* to a small volume, and the residue was extracted with $CHCl_3$. The $CHCl_3$ extracts were washed with H_2O, dried, and concentrated to leave **10a** (200 mg, 86%) as colorless prisms, mp 174—177 °C. This sample was identical [by comparison of the IR spectrum and thin-layer chromatographic (TLC) mobility] with the one described above under item (i).

1-[2-Ethoxy-2-(1*H*-indol-3-yl)ethyl]-2-piperidinone (13)——A solution of **10a** (258 mg, 1 mmol) in abs. EtOH (40 ml) containing 0.02 N aqueous HCl (2.1 ml) was stirred at 25 °C for 1 h. After addition of 10% aqueous Na_2CO_3 (1 ml), the reaction mixture was concentrated *in vacuo*. The residue was dissolved in CH_2Cl_2 (25 ml), and the CH_2Cl_2 solution was washed with H_2O, dried, and concentrated to leave **13** (270 mg, 94%) as yellowish crystals, mp 137—138 °C. Recrystallization from MeCN yielded an analytical sample as colorless prisms, mp 138—139 °C; MS *m/z*: 286 (M^+); UV λ_{max}^{EtOH} 274 nm (ε 6100), 282 (6400), 290 (5700); IR ν_{max}^{Nujol} cm^{-1}: 3320 (NH), 1627 (lactam CO); NMR ($CDCl_3$) δ: 1.13 (3H, t, J=7 Hz, $OCH_2\underline{Me}$), 1.45—1.90 (4H, m, $H_{(4)}$'s and $H_{(5)}$'s), 2.20—2.55 (2H, m, $H_{(3)}$'s), 2.85—4.00 [6H, m, $H_{(6)}$'s, $CH(OEt)C\underline{H}_2N$, and $OC\underline{H}_2Me$], 4.85—5.06 [1H, m, $C\underline{H}(OEt)CH_2N$], 6.88—7.88 (5H, m, aromatic protons), 9.09 (1H, br s, NH). *Anal.* Calcd for $C_{17}H_{22}N_2O_2$: C, 71.30; H, 7.74; N, 9.78. Found: C, 71.29; H, 7.87; N, 9.87.

1-[2-(1*H*-Indol-3-yl)ethyl]-2-piperidinone (9a)——i) From **10a**: A solution of **10a** (517 mg, 2 mmol) in EtOH (100 ml) containing 70% aqueous $HClO_4$ (0.02 ml, *ca.* 0.2 mmol) was hydrogenated over 10% Pd–C (400 mg) at 20 °C and atmospheric pressure for 50 min. The catalyst was removed by filtration, and the filtrate, after addition of 10% aqueous Na_2CO_3 (1 ml), was concentrated *in vacuo*. The residue was partitioned by extraction with a mixture of H_2O (10 ml) and CH_2Cl_2 (25 ml). The CH_2Cl_2 extracts were washed with H_2O, dried, and concentrated to leave **9a** (467 mg, 96%) as a colorless solid, mp 144—148 °C. Recrystallization of the solid from benzene provided a pure sample as colorless prisms, mp 155—156 °C (lit.[7] mp 154.5—155.5 °C). This sample was identical (by mixture melting point test and comparison of the IR spectrum and TLC mobility) with authentic **9a**.[7]

ii) From **13**: A solution of **13** (573 mg, 2 mmol) in EtOH (25 ml) containing 70% aqueous $HClO_4$ (0.02 ml, *ca.* 0.2 mmol) was hydrogenated over 10% Pd–C (500 mg) at 17 °C and atmospheric pressure for 1 h. The reaction mixture was worked up in a manner similar to that described above under item (i), giving **9a** (454 mg, 94%), mp 149—150.5 °C. Recrystallization from benzene afforded a pure sample as colorless prisms, mp 153.5—154.5 °C. This sample was identical (by comparison of the IR spectrum and TLC mobility) with authentic **9a**.[7]

(±)-1,2,3,4,6,7,12,12b-Octahydroindolo[2,3-*a*]quinolizine (1)——This was synthesized from **9a** according to the literature procedure,[7] but with a slight modification. A solution of **9a** (484 mg, 2 mmol) and $POCl_3$ (2.5 ml) in dry benzene (16 ml) was heated under reflux for 75 min. The reaction mixture was concentrated *in vacuo* to leave a yellow solid, which was dissolved in MeOH (15 ml). The methanolic solution was stirred under ice-cooling, and $NaBH_4$ (379 mg, 10 mmol) was added portionwise. After the mixture had been stirred at room temperature for 1 h, acetone (3 ml) was added. The resulting mixture was concentrated *in vacuo* to leave a yellowish solid, which was partitioned by extraction with a mixture of H_2O (7 ml) and CH_2Cl_2 (15 ml). The CH_2Cl_2 extracts were washed with saturated aqueous NaCl, dried, and concentrated to leave **1** (431 mg, 95%) as a yellowish solid, mp 148.5—149.5 °C. Recrystallization from hexane–benzene (3 : 1, v/v) gave a pure sample as colorless prisms, mp 152.5—153.5 °C (lit.[10e] mp 153—154 °C). This sample was identical (by mixture melting point test and comparisons of the IR and NMR spectra and TLC mobility) with authentic **1**.[7]

(±)-*trans*-5-Ethyl-1-[2-(1*H*-indol-3-yl)-2-oxoethyl]-2-oxo-4-piperidineacetic Acid Ethyl Ester (7b)——A mixture of **6b**[12] (2.72 g, 11 mmol), 3-(chloroacetyl)indole[19] (1.94 g, 10 mmol), and KBr (2.86 g, 24 mmol) in $HCONMe_2$ (12 ml) was stirred at 60 °C for 38 h. After addition of H_2O (80 ml), the reaction mixture was extracted with AcOEt. The AcOEt extracts were washed with H_2O, dried, and concentrated to leave a brown oil. The oil was crystallized from AcOEt to yield **7b** (1.50 g) as slightly brownish prisms, mp 133.5—134.5 °C. The mother liquor of this crystallization was then concentrated *in vacuo*, and the residue was purified by means of column chromatography [silica gel, AcOEt–EtOH (95 : 5, v/v)] followed by recrystallization from AcOEt, giving a second crop (1.08 g) of **7b**. The total yield was 2.58 g [70% yield based on the 3-(chloroacetyl)indole used]. Further recrystallizations from AcOEt afforded an analytical sample as colorless prisms, mp 135—136 °C; MS *m/z*: 370 (M^+); UV λ_{max}^{EtOH} 241.5 nm (ε 15500), 260 (sh) (9200), 299 (12700); IR ν_{max}^{Nujol} cm^{-1}: 3140 (NH), 1717 (ester CO), 1658 (ArCO), 1610 (lactam CO); NMR ($CDCl_3$) δ: 0.92 (3H, t, J=7 Hz, $CCH_2\underline{Me}$), 1.26 (3H, t, J=7 Hz, $OCH_2\underline{Me}$), 1.38—3.52 (10H, m, $C\underline{H}_2Me$, $H_{(3)}$'s, $H_{(4)}$, $H_{(5)}$, $H_{(6)}$'s, and $C\underline{H}_2CO_2Et$), 4.14 (2H, q, J=7 Hz, $OC\underline{H}_2Me$), 4.35 (2H, s, $COCH_2N$), 7.12—8.32 (5H, m, aromatic protons), 10.64 (1H, br s, NH). *Anal.* Calcd for $C_{21}H_{26}N_2O_4$: C, 68.09; H, 7.07; N, 7.56. Found: C, 68.25; H,

7.32; N, 7.84.

(±)-*trans*-5-Ethyl-1-[2-hydroxy-2-(1*H*-indol-3-yl)ethyl]-2-oxo-4-piperidineacetic Acid Ethyl Ester (10b)——A solution of **7b** (2.22 g, 6 mmol) in EtOH (200 ml) was stirred under ice-cooling and $NaBH_4$ (5.68 g, 150 mmol) was added portionwise. After the mixture had been stirred at 22—25 °C for 3 h, acetone (36 ml) was added under ice-cooling. The resulting mixture was stirred for a while and then concentrated *in vacuo*. The residue was treated with H_2O (200 ml), and the aqueous mixture was neutralized with 10% aqueous HCl and extracted with CH_2Cl_2. The CH_2Cl_2 extracts were washed with H_2O, dried, and concentrated to leave a yellowish solid (2.06 g). Recrystallization of the solid from AcOEt gave **10b** (1.56 g, 70%) as colorless needles, mp 120.5—122.5 °C, which were presumed to be a mixture of the two possible diastereomeric alcohols. Further recrystallizations from AcOEt furnished an analytical sample, but of unknown stereochemical purity, as colorless small needles, mp 122—123 °C; MS *m/z*: 372 (M^+); UV λ_{max}^{EtOH} 273.5 nm (sh) (ε 5700), 282 (6100), 289.5 (5200); IR ν_{max}^{Nujol} cm^{-1}: 3260 (NH and OH), 1730 (ester CO), 1621 (lactam CO); NMR ($CDCl_3$) δ: 0.48—0.88 (3H, m, diastereomeric $CCH_2\underline{Me}$'s), 1.22 (3H, t, $J=7$ Hz, $OCH_2\underline{Me}$), 1.60—3.76 (10H, m, $CC\underline{H}_2Me$, $H_{(3)}$'s, $H_{(4)}$, $H_{(5)}$, $H_{(6)}$'s, and $C\underline{H}_2CO_2Et$), 4.12 (2H, q, $J=7$ Hz, $OC\underline{H}_2Me$), 4.00—4.32 (1H, br, OH), 5.16—5.40 [1H, m, diastereomeric $C\underline{H}(OH)CH_2N$'s], 6.90—7.76 (5H, m, aromatic protons), 8.60 (1H, br s, NH). *Anal.* Calcd for $C_{21}H_{28}N_2O_4$: C, 67.72; H, 7.58; N, 7.52. Found: C, 67.98; H, 7.67; N, 7.73.

(±)-*trans*-5-Ethyl-1-[2-(1*H*-indol-3-yl)ethyl]-2-oxo-4-piperidineacetic Acid Ethyl Ester (9b)——A solution of **10b** (745 mg, 2 mmol) in EtOH (25 ml) containing 70% aqueous $HClO_4$ (0.02 ml, *ca.* 0.2 mmol) was hydrogenated over 10% Pd–C (600 mg) at 21—22 °C and atmospheric pressure for 1 h. The catalyst was removed by filtration, and the filtrate, after addition of 10% aqueous Na_2CO_3 (2 drops), was concentrated *in vacuo*. The residue was partitioned by extraction with a mixture of H_2O (20 ml) and CH_2Cl_2 (80 ml). The CH_2Cl_2 extracts were washed with H_2O, dried, and concentrated to leave a reddish brown oil. Purification of the oil by column chromatography [silica gel (5 g), AcOEt] gave **9b** (529 mg, 74%) as a slightly yellowish solid, mp 102.5—103.5 °C. Recrystallization from diisopropyl ether–AcOEt (2 : 1, v/v) yielded an analytical sample as colorless prisms, mp 107—108 °C [lit.[13b] mp 108—110 °C (uncor.)]; MS *m/z*: 356 (M^+); UV λ_{max}^{EtOH} 276.5 nm (sh) (ε 5300), 284 (5800), 292 (5200); IR ν_{max}^{Nujol} cm^{-1}: 3140, 3100 (NH), 1722 (ester CO), 1623 (lactam CO); NMR ($CDCl_3$) δ: 0.74 (3H, t, $J=7$ Hz, $CCH_2\underline{Me}$), 1.24 (3H, t, $J=7$ Hz, $OCH_2\underline{Me}$), 1.80—3.28 (12H, m, $CC\underline{H}_2Me$, $ArC\underline{H}_2$, $H_{(3)}$'s, $H_{(4)}$, $H_{(5)}$, $H_{(6)}$'s, and $C\underline{H}_2CO_2Et$), 3.40—3.60 (2H, m, $ArCH_2C\underline{H}_2$), 4.14 (2H, q, $J=7$ Hz, $OC\underline{H}_2Me$), 6.88—7.76 (5H, m, aromatic protons), 8.40 (1H, br s, NH). *Anal.* Calcd for $C_{21}H_{28}N_2O_3$: C, 70.76; H, 7.92; N, 7.86. Found: C, 70.72; H, 7.90; N, 8.03. This sample was identical (by mixture melting point test and comparison of the IR spectrum and TLC mobility) with authentic **9b**.[13]

Acknowledgment We are grateful to Professor E. E. van Tamelen (Stanford University) for a valuable supply of a sample of the (±)-*trans*-lactam ester **9b**, to Professor T. Hino (Chiba University) for a generous gift of the lactam **9a** and the (±)-tetracyclic base **1**, and to Dr. M. Ohba (Kanazawa University) for clerical assistance in preparing the manuscript.

References and Notes

1) Paper XXIV in this series, T. Fujii and M. Ohba, *Chem. Pharm. Bull.*, **36**, 2665 (1988).
2) *a*) G. A. Cordell and J. E. Saxton, "The Alkaloids," Vol. 20, ed. by R. H. F. Manske and R. G. A. Rodrigo, Academic Press, New York, 1981, Chapter 1; *b*) Atta-ur-Rahman and A. Basha, "Biosynthesis of Indole Alkaloids," Clarendon Press, Oxford, 1983; *c*) C. Szántay, G. Blaskó, K. Honty, and G. Dörnyei, "The Alkaloids," Vol. 27, ed. By A. Brossi, Academic Press, New York, 1986, Chapter 2.
3) *a*) T. Fujii, S. Yoshifuji, and K. Yamada, *Chem. Pharm. Bull.*, **26**, 2071 (1978); *b*) T. Fujii, M. Ohba, K. Yoneyama, H. Kizu, and S. Yoshifuji, *ibid.*, **34**, 669 (1986), and references cited therein; *c*) T. Fujii, M. Ohba, K. Shimohata, and S. Yoshifuji, *Heterocycles*, **26**, 2949 (1987); *d*) For a recent review, see T. Fujii, M. Ohba, and S. Yoshifuji, *ibid.*, **27**, 1009 (1988).
4) For reviews, see *a*) T. Fujii and M. Ohba, "The Alkaloids," Vol. 22, ed. by A. Brossi, Academic Press, New York, 1983, Chapter 1; *b*) T. Fujii, *Yakugaku Zasshi*, **103**, 257 (1983).
5) A preliminary account of this work has been published: T. Fujii, S. Yosifuji, and H. Ito, *Heterocycles*, **7**, 149 (1977).
6) T. Oishi, M. Nagai, T. Onuma, H. Moriyama, K. Tsutae, M. Ochiai, and Y. Ban, *Chem. Pharm. Bull.*, **17**, 2306 (1969).
7) M. Nakagawa, M. Kiuchi, M. Obi, M. Tonozuka, K. Kobayashi, T. Hino, and Y. Ban, *Chem. Pharm. Bull.*, **23**, 304 (1975).
8) R. J. Sundberg, "The Chemistry of Indoles," Academic Press, New York, 1970, pp. 93—107.
9) *a*) S. R. Johns, J. A. Lamberton, and J. L. Occolowitz, *Chem. Commun.*, **1966**, 421; *b*) *Idem, Aust. J. Chem.*, **19**, 1951 (1966).
10) *a*) Ref. 10 in ref. 7; *b*) S. Yamada and T. Kunieda, *Chem. Pharm. Bull.*, **15**, 499 (1967); *c*) L. Novák and C. Szántay, *Chem. Ber.*, **102**, 3959 (1969); *d*) C. A. Scherer, C. A. Dorschel, J. M. Cook, and P. W. Le Quesne, *J. Org. Chem.*, **37**, 1083 (1972); *e*) G. W. Gribble, *ibid.*, **37**, 1833 (1972); *f*) H.-P. Husson, L. Chevolot, Y. Langlois,

C. Thal, and P. Potier, *J. Chem. Soc., Chem. Commun.*, **1972**, 930; *g*) H. Akimoto, K. Okamura, M. Yui, T. Shioiri, M. Kuramoto, Y. Kikugawa, and S. Yamada, *Chem. Pharm. Bull.*, **22**, 2614 (1974); *h*) E. E. van Tamelen, J. Webber, G. P. Schiemenz, and W. Barker, *Bioorg. Chem.*, **5**, 283 (1976); *i*) S. Yamada, K. Murato, and T. Shioiri, *Tetrahedron Lett.*, **1976**, 1605; *j*) S. J. Martinez and J. A. Joule, *Tetrahedron*, **34**, 3027 (1978); *k*) E. Yamanaka, K. Nakayama, N. Yanagishima, K. Nagashima, M. Yamauchi, and S. Sakai, *Chem. Pharm. Bull.*, **28**, 2527 (1980); *l*) J. E. Johansen, B. D. Christie, and H. Rapoport, *J. Org. Chem.*, **46**, 4914 (1981); *m*) T. Fujii, M. Ohba, and N. Sasaki, *Heterocycles*, **22**, 1805 (1984); *n*) A. I. Meyers, T. Sohda, and M. F. Loewe, *J. Org. Chem.*, **51**, 3108 (1986); *o*) G. W. Gribble and D. A. Johnson, *Tetrahedron Lett.*, **28**, 5259 (1987).

11) *a*) S. Sugasawa and T. Fujii, *Pharm. Bull.*, **3**, 47 (1955); *b*) T. Fujii, *Chem. Pharm. Bull.*, **6**, 591 (1958); *c*) T. Fujii, S. Yoshifuji, and M. Tai, *ibid.*, **23**, 2094 (1975); *d*) T. Fujii, S. Yoshifuji, and M. Ohba, *ibid.*, **26**, 645 (1978); *e*) T. Fujii, H. Kogen, S. Yoshifuji, and K. Iga, *ibid.*, **27**, 1847 (1979); *f*) T. Date, K. Aoe, M. Ohba, and T. Fujii, *Yakugaku Zasshi*, **99**, 865 (1979); *g*) T. Fujii, S. Yoshifuji, and K. Ikeda, *Chem. Pharm. Bull.*, **27**, 2841 (1979).

12) *a*) M. Uskoković, C. Reese, H. L. Lee, G. Grethe, and J. Gutzwiller, *J. Am. Chem. Soc.*, **93**, 5902 (1971); *b*) J. Gutzwiller, G. Pizzolato, and M. R. Uskoković, *Helv. Chim. Acta*, **64**, 1663 (1981); *c*) T. Fujii and S. Yoshifuji, *Chem. Pharm. Bull.*, **27**, 1486 (1979).

13) *a*) E. E. van Tamelen and J. B. Hester, Jr., *J. Am. Chem. Soc.*, **81**, 3805 (1959); *b*) *Idem, ibid.*, **91**, 7342 (1969).

14) J. A. Weisbach, J. L. Kirkpatrick, K. R. Williams, E. L. Anderson, N. C. Yim, and B. Douglas, *Tetrahedron Lett.*, **1965**, 3457.

15) C. Szántay and M. Bárczai-Beke, *Chem. Ber.*, **102**, 3963 (1969).

16) J. P. Kutney and R. T. Brown, *Tetrahedron*, **22**, 321 (1966).

17) T. R. Govindachari and S. Rajeswari, *Indian J. Chem.*, **22B**, 531 (1983).

18) T. Fujii, M. Ohba, T. Tachinami, H. Miyajima, M. Koch, and E. Seguin, *Heterocycles*, **24**, 1215 (1986).

19) *a*) J. Bergman, *J. Heterocycl. Chem.*, **7**, 1071 (1970); *b*) J. Bergman, J.-E. Bäckvall, and J.-O. Lindström, *Tetrahedron*, **29**, 971 (1973).